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FILE LAST UPDATED: 20 Jun 2008  (20080620/ED)

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=> autologous transformation
         17214 AUTOLOGOUS
        369140 TRANSFORMATION
         83790 TRANSFORMATIONS
        423083 TRANSFORMATION
                (TRANSFORMATION OR TRANSFORMATIONS)
L1           0 AUTOLOGOUS TRANSFORMATION
                (AUTOLOGOUS(W)TRANSFORMATION)

=> (GM CSF)
         29242 GM
          1063 GMS
         30189 GM
                (GM OR GMS)
         41733 CSF
           685 CSFS
         41842 CSF
                (CSF OR CSFS)
L2       14050 (GM CSF)
                (GM(W)CSF)

=> autologous
L3       17214 AUTOLOGOUS

=> L3 and L2
L4         629 L3 AND L2

=> EBV
          9126 EBV
```

```
            40 EBVS
L5        9134 EBV
                 (EBV OR EBVS)

=> L3 and L5
L6         366 L3 AND L5

=> antigen (w) specific
         339010 ANTIGEN
         266361 ANTIGENS
         427273 ANTIGEN
                 (ANTIGEN OR ANTIGENS)
        1500682 SPECIFIC
           1770 SPECIFICS
        1502253 SPECIFIC
                 (SPECIFIC OR SPECIFICS)
         318132 SP
           9186 SPS
         326849 SP
                 (SP OR SPS)
        1788105 SPECIFIC
                 (SPECIFIC OR SP)
L7        16268 ANTIGEN (W) SPECIFIC

=> L7 and L6
L8           43 L7 AND L6

=> (MHC-1)
          42042 MHC
            276 MHCS
          42062 MHC
                 (MHC OR MHCS)
        9676075 1
L9          128 (MHC-1)
                 (MHC(W)1)

=> L9 and L8
L10           0 L9 AND L8

=> EBV (w) specific
           9126 EBV
             40 EBVS
           9134 EBV
                 (EBV OR EBVS)
        1500682 SPECIFIC
           1770 SPECIFICS
        1502253 SPECIFIC
                 (SPECIFIC OR SPECIFICS)
         318132 SP
           9186 SPS
         326849 SP
                 (SP OR SPS)
        1788105 SPECIFIC
                 (SPECIFIC OR SP)
L11         531 EBV (W) SPECIFIC

=> L11 and L8
L12           7 L11 AND L8

=> D L12 IBIB ABS 1-7
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L12 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:731704 CAPLUS
DOCUMENT NUMBER: 145:374919
TITLE: CD28 co-stimulation via tumour-specific chimaeric receptors induces an incomplete activation response in Epstein-Barr virus-specific effector memory T cells
AUTHOR(S): Altvater, B.; Pscherer, S.; Landmeier, S.; Niggemeier, V.; Juergens, H.; Vormoor, J.; Rossig, C.
CORPORATE SOURCE: Department of Paediatric Haematology and Oncology, University Children's Hospital Muenster, Muenster, Germany
SOURCE: Clinical and Experimental Immunology (2006), 144(3), 447-457
CODEN: CEXIAL; ISSN: 0009-9104
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Expression of tumor antigen-specific chimeric receptors in T lymphocytes can redirect their effector functions towards tumor cells. Integration of the signalling domains of the co-stimulatory mol. CD28 into chRec enhances antigen-specific proliferation of polyclonal human T cell populations. While CD28 plays an essential role in the priming of naive CD4+ T cells, its contribution to effector memory T cell responses is controversial. We compared the function of the chRec with and without the CD28 co-stimulatory domain, expressing it in peripheral blood T cells or Epstein-Barr virus (EBV)-specific T cell lines. The chimaeric T cell receptors contain an extracellular single-chain antibody domain, to give specificity against the tumor ganglioside antigen GD2. The transduced cytotoxic T lymphocytes (CTL) maintained their specificity for autologous EBV targets and their capacity to proliferate after stimulation with EBV-infected B cells. Intracellular cytokine staining demonstrated efficient and comparable antigen-specific interferon (IFN)-γ secretion by CTL following engagement of both the native and the chimaeric receptor, independent of chimaeric CD28 signalling. Furthermore, tumor targets were lysed in an antigen-specific manner by both chRec. However, while antigen engagement by CD28ζ chRec efficiently induced expansion of polyclonal peripheral blood lymphocytes in an antigen-dependent manner, CD28 signalling did not induce proliferation of EBV-CTL in response to antigen-expressing tumor cells. Thus, the co-stimulatory requirement for the efficient activation response of antigen-specific memory cells cannot be mimicked simply by combining CD28 and ζ signalling. The full potential of this highly cytolytic T cell population for adoptive immunotherapy of cancer requires further exploration of their co-stimulatory requirements.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:1323573 CAPLUS
DOCUMENT NUMBER: 145:143232
TITLE: Target Antigen Expression on a Professional Antigen-Presenting Cell Induces Superior Proliferative Antitumor T-Cell Responses via Chimeric T-Cell Receptors
AUTHOR(S): Rossig, Claudia; Baer, Annette; Pscherer, Sibylle; Altvater, Bianca; Pule, Martin; Rooney, Cliona M.; Brenner, Malcolm K.; Juergens, Heribert; Vormoor, Josef
CORPORATE SOURCE: Department of Pediatric Hematology and Oncology,

University Children's Hospital Muenster, Muenster, Germany
SOURCE: Journal of Immunotherapy (2005), Volume Date 2006, 29(1), 21-31
CODEN: JOIMF8; ISSN: 1524-9557
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Human T cells expressing tumor antigen-specific chimeric receptors fail to sustain their growth and activation in vivo, which greatly reduces their therapeutic value. The defective proliferative response to tumor cells in vitro can partly be overcome by concomitant CD28 costimulatory signaling. We investigated whether T-cell activation via chimeric receptors (chRec) can be further improved by ligand expression on antigen-presenting cells of B-cell origin. We generated Epstein-Barr virus (EBV)-specific cytotoxic T lymphocytes (CTLs) expressing a CD19-specific chRec. These CTLs are provided with native receptor stimulation by autologous EBV-transformed B-lymphoblastoid cell lines (LCLs) but exclusively with chRec (CD19-specific) stimulation by allogeneic, human leukocyte antigen (HLA)-mismatched CD19 LCLs. CD19ζ-transduced EBV-specific CTLs specifically lysed both allogeneic EBV targets and CD19 tumor cells through the chRec in a major histocompatibility complex-independent manner, while maintaining their ability to recognize autologous EBV targets through the native T-cell receptor. The transduced CTLs failed to proliferate in response to CD19 tumor targets even in the presence of CD28 costimulatory signaling. By contrast, CD19 expressed on HLA-mismatched LCL-induced T-cell activation and long-term proliferation that essentially duplicated the result from native receptor stimulation with autologous LCLs, suggesting that a deficit of costimulatory mols. on target cells in addition to CD28 is indeed responsible for inadequate chRec-mediated T-cell function. Hence, effective tumor immunotherapy may be favored if engagement of the chRec on modified T cells is complemented by interaction with multiple costimulator mols. The use of T cells with native specificity for EBV may be one means of attaining this objective.
REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2000:446029 CAPLUS
DOCUMENT NUMBER: 133:175812
TITLE: Rapid selection of antigen-specific T lymphocytes by retroviral transduction
AUTHOR(S): Koehne, Guenther; Gallardo, Humilidad F.; Sadelain, Michel; O'Reilly, Richard J.
CORPORATE SOURCE: Bone Marrow Transplant Service, Department of Pediatrics, Memorial Hospital, New York, NY, USA
SOURCE: Blood (2000), 96(1), 109-117
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: American Society of Hematology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Infusions of donor peripheral blood T cells can induce durable remissions of Epstein-Barr virus (EBV) lymphomas complicating marrow grafts, but they contain alloreactive T cells capable of inducing graft-vs.-host disease. EBV-specific T-cell lines or clones avoid this problem but require 30 to 40 days of culture to establish. To accelerate the generation of EBV-specific T cells, the authors tested whether retroviral vectors, which only

integrate in dividing cells, could be used to transduce and select antigen-reactive T cells early after sensitization to autologous EBV-transformed B cells. T cells were transduced with a dicistronic retroviral vector, NIT, which encodes low-affinity nerve growth factor receptor as an immunoselectable marker and herpes simplex virus thymidine kinase as a suicide gene, at different time points after sensitization. EBV-specific cytotoxic T lymphocyte precursor (CTLp) frequencies in purified NIT+ T-cell fractions transduced on day 8 of culture were comparable to those of EBV-specific T-cell lines cultured for 30 days or more. Alloreactive CTLp frequencies were markedly reduced in the NIT+ fraction relative to the untransduced T-cell population. NIT+ fractions transduced on day 8 possessed more CD4+ T cells than the cell lines at day 30 and exhibited the same selective pattern of reactivity against immunodominant antigens presented by specific HLA alleles. In contrast, T cells transduced with NIT 5 days after stimulation with mitogen and interleukin-2 were relatively depleted of T cells specific for autologous EBV-transformed cells. Thus, retroviral vectors may be used for rapid selection of viral antigen-reactive T cells depleted of alloreactive T cells.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1999:510205 CAPLUS

DOCUMENT NUMBER: 131:298605

TITLE: CD4+ Epstein-Barr Virus-Specific Cytotoxic T-Lymphocytes from Human Umbilical Cord Blood

AUTHOR(S): Sun, Qi; Burton, Robert L.; Pollok, Karen E.; Emanuel, David J.; Lucas, Kenneth G.

CORPORATE SOURCE: Bone Marrow Transplantation Program, University of Alabama at Birmingham, Birmingham, AL, 35294, USA

SOURCE: Cellular Immunology (1999), 195(2), 81-88
CODEN: CLIMB8; ISSN: 0008-8749

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Umbilical cord blood (CB) is increasingly used for allogeneic hematopoietic stem cell transplantation. To determine whether viral antigen-specific cytotoxic T-lymphocytes (CTL) could be generated from the predominantly naive T-cell populations in CB, CB-derived mononuclear cells were stimulated with autologous Epstein-Barr virus (EBV) transformed B-lymphoblastoid cell lines over several weeks in the presence of recombinant human interleukin-2 (IL-2). By 28 days of culture, T-lymphocytes from all six CB that had been treated with IL-2 displayed EBV-specific cytotoxicity. These cells were largely CD4+, with complete inhibition of cytotoxicity by anti-CD3 and variable inhibition by anti-HLA DR monoclonal antibodies. The EBV-specific effectors were cloned by limiting dilution, and most of the CTL clones were CD4+. The cytotoxicity of the CB-derived CD4+ CTL clones was inhibited by EGTA but not by anti-Fas ligand mAb, suggesting that this cytotoxicity was mediated by perforin/granzyme B. These data indicate that virus-specific CTL can be cultivated and cloned from CB, a human T-cell source that may not have prior in vivo antigenic exposure or reactivity. This finding may have applications in adoptive immunotherapy to recipients of CB transplants. (c) 1999 Academic Press.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1999:470533 CAPLUS
TITLE: Increased frequency of antigen-specific CD8+ cytotoxic T lymphocytes infiltrating an Epstein-Barr virus-associated gastric carcinoma
AUTHOR(S): Kuzushima, Kiyotaka; Nakamura, Shigeo; Nakamura, Tsuneya; Yamamura, Yoshitaka; Yokoyama, Naoaki; Fujita, Masatoshi; Kiyono, Tohru; Tsurumi, Tatsuya
CORPORATE SOURCE: Laboratory of Viral Oncology, Aichi Cancer Center Research Institute, Nagoya, 464-0021, Japan
SOURCE: Journal of Clinical Investigation (1999), 104(2), 163-171
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: American Society for Clinical Investigation
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Gastric adenocarcinomas carrying Epstein-Barr virus (EBV) are known to be accompanied by massive lymphocyte infiltration. To characterize the tumor-infiltrating lymphocytes (TILs), we isolated and cultured such cells from a surgically resected EBV-associated gastric carcinoma. They were found to be pos. for CD3, CD8, T-cell receptor β chain, and cytotoxic mols. The isolated TILs consisted of human leukocyte antigen (HLA) class I-restricted CD8+ cytotoxic T lymphocytes (CTLs), which killed autologous EBV -transformed cells (but not phytohemagglutinin blast cells) and recognized HLA-A24 as restriction mols. However, the TILs did not recognize known EBV antigenic peptides presented by HLA-A24 mols., nor HLA-A24+ fibroblasts infected with vaccinia recombinant virus expressing each of the EBV latent proteins. EBV+ gastric carcinomas do not express conventional target proteins of EBV-specific CTLs, and the data suggest that some cellular proteins may be involved in the strong T-cell response to EBV-associated gastric carcinoma. In addition, our data suggest that class I-restricted, antigen-specific CD8+ CTLs are specifically expanded within EBV+ gastric carcinoma tissue.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1998:340934 CAPLUS
DOCUMENT NUMBER: 129:66714
ORIGINAL REFERENCE NO.: 129:13845a,13848a
TITLE: Immunotherapy for Epstein-Barr virus-associated cancers
AUTHOR(S): Rooney, Cliona M.; Roskrow, Marie A.; Smith, Colton A.; Brenner, Malcolm K.; Heslop, Helen E.
CORPORATE SOURCE: Department of Virology and Molecular Biology, St. Jude Children's Research Hospital, Memphis, TN, USA
SOURCE: Journal of the National Cancer Institute Monographs (1998), 23, 89-93
CODEN: JNCME4; ISSN: 1052-6773
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Epstein-Barr virus (EBV)-associated lymphoproliferative disease (EBV-LPD) is a frequently fatal complication of organ transplantation and human immunodeficiency virus (HIV) infection. We have studied the safety and efficacy of adoptively transferred, gene-marked virus-specific cytotoxic T lymphocytes (CTLs) as prophylaxis and treatment of EBV-LPD in recipients of T-cell-depleted allogeneic bone marrow. In 42 patients treated prophylactically, no toxicity was

experienced. None of these patients developed EBV-LPD, in contrast with eight of 53 (15%) patients who did not receive prophylactic CTL. Three patients who had not received CTL developed aggressive disease and received CTL as treatment. Gene-marked CTL homed to tumor sites and selective accumulation of marker gene was detected in tumor tissues. Tumors regressed completely in two patients, but the third died of respiratory failure. Infused CTLs persisted for up to 3 yr in vivo, they rapidly reconstituted EBV-specific immune responses to levels seen in normal individuals, and they reduced high viral titers by two to three logs. We are now using autologous EBV-specific CTL to treat patients with relapsed EBV-pos. Hodgkin's disease and we are developing methods for the generation of antigen-specific lines. This approach could be applied to patients with HIV who develop EBV-LPD, using CTL derived early in the course of HIV infection.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1995:204314 CAPLUS

TITLE: CD8high(CD57+) T cells in normal, healthy individuals specifically suppress the generation of cytotoxic T lymphocytes to Epstein-Barr virus-transformed B cell lines

AUTHOR(S): Wang, Eddie Chung Yern; Lehner, Paul Joseph; Graham, Shek; Borysiewicz, Leszek Krysztof

CORPORATE SOURCE: Dep. Medicine, Univ. Wales College Medicine, Cardiff, UK

SOURCE: European Journal of Immunology (1994), 24(11), 2903-2909
CODEN: EJIMAF; ISSN: 0014-2980

PUBLISHER: VCH

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We have previously identified two subsets of CD8+, CD57+ lymphocytes in normal peripheral blood: (1) T cells expressing high levels [CD8high(CD57+)] and (2) natural killer cells expressing low levels of surface CD8[CD8low(CD57+)]. We investigated the cytotoxic and suppressive function of CD8high(CD57+) T lymphocytes from normal, healthy individuals using standard chromium-release assays and limiting dilution anal. In normal, healthy subjects, this cell subset suppressed the generation of cytotoxic T lymphocytes (CTL) to autologous, Epstein-Barr virus (EBV)-transformed B cell lines (BCL). Depletion of CD8high(CD57-) T lymphocytes from peripheral blood mononuclear cells (PBMC) resulted in a three- to sevenfold rise in CTL precursor frequency to autologous EBV-transformed BCL, but not allogeneic PBMC or BCL by LDA. Replacement of CD8high(CD57+) T lymphocytes in limiting dilution cultures led to the dose-dependent suppression of EBV-specific, but not allogeneic, CTL generation. Supernatant from CD8high(CD57+) T lymphocytes cultured with autologous BCL did not exhibit suppression, suggesting that soluble factors were not responsible. As CD8high(CD57+) T lymphocytes did not, themselves, exhibit cytotoxicity against autologous BCL, removal of BCL stimulator cells in co-culture was not the mechanism of suppression. Furthermore, while the CD8high(CD57+) T lymphocytes from healthy subjects suppressed the generation of CTL to autologous BCL, they did not suppress the cytotoxic activity of established mixed lymphocyte reactions or peptide-specific CTL clones, as has been reported in bone marrow transplant recipients and human immunodeficiency virus patients. This suggests that CD8high(CD57+) T lymphocytes from healthy subjects suppress the generation of, rather than killing by, CTL in a contact-dependent

manner. To our knowledge, this is the first identification of a phenotypically distinct subset of human CD8+ T cells that can suppress generation of antigen-specific major histocompatibility complex class I-restricted CTL.